Polyneuropathies and myopathies in SSA children: diagnostics, neurogenetics and therapeutic management

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Topics

• Not just genetics....

• What is relevant / prevalent in LMICs?
• How does this relate to care?
• What should standard care be?
• What are future priorities?
What is relevant / prevalent in LMICs?
Neuromuscular diseases in LMIC - Africa

Using search terms “neuromuscular disease” “children” “Africa”

Main results:-
• Infections
  • Polio
  • Enteroviruses
• Secondary complications
  • HIV
  • Erroneous injection sites
• Nutritional conundrums
  • Konzo / cassava

Very little on genetic disorders..........
Neuromuscular clinic stats

- AMC
- SMA
- Distal SMA
- Peripheral neuropathy
- Myasthenia gravis
- Myopathies
- DMD/BMD
- Distal MD
- FSHMD
- LGMD
- Congenital dystrophy
- Bethlem myopathy
- Rigid spine MD
- Myotonia
- Dermatomyositis
- AIDP/CIDP
- Miscellaneous
where are the genetic disorders?
Realities and Challenges

- In most RPC the prevalence of NMD (communicable / non-communicable / genetic) is not known
  - The true burden is not defined
  - This challenges motivation for adequate services

- Related to
  - Limited clinical skills
    - many patients are mislabelled with cerebral palsy
  - Lack of access to diagnostic tools
    - from CSF to CK to muscle biopsy to molecular genetics
  - Limited access to trained rehabilitation therapists and orthotic centres
INFECTIONS
Poliomyelitis
Spectrum of Disease – Entire Neuraxis

**Clinical**
- Asymptomatic (90 – 95%)
- Abortive poliomyelitis (4 -8%)
- Non-paralytic polio (1 – 5%)
- Paralytic (spinal; bulbar; bulbospinal) <2%

**Encephalitis**
- Cerebellitis
- Striatal necrosis (IBSN)
- Brainstem encephalitis
- Myelitis (ATM)
- Radiculoneuritis
- (Myositis)
Polio Eradication: World Health Assembly–2008-2012

Fig. 1. Countries with indigenous poliovirus circulation versus the initiation of national eradication efforts, 1985–2006.
History

• **WHA voted in 1988** for Global Polio Eradication Programme

• **Then:**
  - 350,000 paralytic cases
    - in 185 countries

• **In 2013:**
  - 3 countries
  - Nigeria, Pakistan, Afghanistan
Milestones of Polio Eradication Process

Figure 1: Containment requirements 2014-2020

1. Essential facilities holding WPV
   - Inventory, destruction, preparation for containment
   - Accreditation

2. Essential facilities holding OPV/Sabin only (no WPV)
   - Destruction, preparation for containment
   - Accreditation

3. Non-essential facilities
   - Destruction, Safe handling, no storage
   - Adoption safe measures

Phase I: Inventory, destruction, preparation for containment of poliovirus type 2

Phase II: Poliovirus type 2 containment period

Phase III: Final poliovirus containment

- Global readiness of withdrawal
- OPV2 withdrawal
- Global eradication certification
- bOPV cessation
- Final containment of all OPV/Sabin polioviruses (primary and secondary safeguards only)
Enteroviruses
Non-polio Enteroviruses

- Enterovirus D68
- Enterovirus A71
Recent upscale in cases enterovirus D68 worldwide
Red Cross War Memorial Children’s Hospital, Cape Town, South Africa

- Acute flaccid paralysis (esp. Asymmetric)
  - Excluding patients with AIDP
- N=14 (April 2012 – September 2015)
- Age range: 1 – 12 years (median 4 years)
- Prodrom (n=12; respiratory/gastroenter.)
- Bulbar-respiratory: n=6
- Enterovirus positive:
  - (n=7; 6 stool – NCID lab / 1 NPA)
Radiculitis
Myeloradiculitis - Asymmetric
Myelitis – anterior grey matter
Myelitis – Anterior Horn Cells
Asymmetrical
### Outcomes of the Red Cross series

- **Survival**  
  - n=14

- **Artificial ventilation**  
  - n=6

- **Residual neurology at discharge**  
  - asymmetric weakness  
    - n=14
  - diaphragm weakness  
    - n=1 (home ventilation)
  - bulbar weakness  
    - n=1

- **Ambulation at discharge**  
  - n=9
Neuroimaging of patients with non-polio enteroviral infections can mimic poliomyelitis

Non-polio enteroviruses
Jang et al Neuroradiology 2012 /Shen et al AmJNeurorad 1999

Polio
Choudhary et al JCN 2010
Overall

- Poliomyelitis is soon becoming extinct......
- But **other enteroviruses** continue to affect children and to cause serious morbidity.
- Modern neuroimaging role in aiding diagnosis.
  - Major challenge for access to imaging in LMICs
- Must keep reporting all cases of Acute Flaccid Paralysis
Secondary neuromuscular diseases
A global view of HIV infection
33.4 million people [31.1–35.8 million] living with HIV, 2008
Including 2.1 million children [1.2-2.9 million]

South Africa, 2008-2009
Total population HIV infected 5.21 M
Children 0-14 280,000
Newly-infected children 59,000
Children on ART 94,000
Estimated ART coverage 61%

HIV

Multiple causes
• Underestimated in children
• Signs may be masked by poor nutritional state
• Paraesthesias and pain most common complaint, then weakness

• Myopathy (rarer in children)
• Vacuolar myelopathy (very rare in children)

• Neuropathy
  • Direct – mutation of Schwann cell nucleus function
  • Opportunistic infection eg cytomegalovirus
  • Adverse effects of antiretroviral therapy eg stavudine (d4t)
    • Convenience sample 78/600 – 6% affected (Govender et al JCN 2011)
Guillain-Barré syndrome

- Common and often severe
  - Typically motor axonal type
  - Diaphragm often involved

- Prolonged hospital stay – tracheostomy / ventilation
  – not viable option elsewhere

- Red Cross experience
  - Prolonged stay
  - 8 children per year
  - Median 4.5 years
  - 31% PICU
    - 28% tracheostomy
  - Mycoplasma, enterovirus commonest identified pathogens
Injection sites

• Acquired foot drop...
• Injections account for 1/5 of all traumatic nerve injuries in LMICs

• Malawian study
• N=50 children with acquired foot drop
• 90% gluteal IM injection of quinine

Namate et al Trop Doc 2012
Shah et al BMJcase reports 2016
Nutritional
Konzo / cassava – Epidemic spastic paraparesis

- Minimal protein intake
- Cassava roots consumption
- Cyanide toxicity

- Prevalent in Nigeria, Tanzania, Sierra Leone, Mozambique, Central African Republic, and Democratic Republic of the Congo.

- 4-12 years and young women.

- Symmetrical spastic paraparesis disease
- Marked sensory polyneuropathy and ataxia.

- Overlap with features of dry beriberi.
- The condition may be result of thiamine deficiency from over consumption of cassava roots.

Genetic conditions
Most commonly seen in SA

- Duchenne muscular dystrophy
- Other MDs (rigid spine, LGMD etc)
- Spinal muscular atrophy
- Congenital myopathies
  - Centronuclear myopathy
- CMT
**Congenital Myopathies**
- Many different types (2008)

<table>
<thead>
<tr>
<th>Myopathy Type</th>
<th>Count</th>
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<tbody>
<tr>
<td>Central core myopathy</td>
<td>n=1</td>
</tr>
<tr>
<td><strong>Centronuclear/ myotubular myopathy</strong></td>
<td>n=14</td>
</tr>
<tr>
<td>Minicore myopathy</td>
<td>n=1</td>
</tr>
<tr>
<td>Nemaline myopathy</td>
<td>n=2</td>
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<tr>
<td>Congenital myopathy</td>
<td>n=4</td>
</tr>
<tr>
<td>Congenital dystrophy</td>
<td>n=7</td>
</tr>
</tbody>
</table>
Ryanodine 1 mutations – 9/11 confirmed

Courtesy of Heinz Jungbluth
Outcome aspects for our patients

*Wilmshurst et al Ann Neurol 2010*

- Centronuclear myopathy is the most prevalent congenital myopathy in Western Cape
- Similar findings across South Africa (personal communication with centres in Gauteng, Kwa-Zulu Natal and Free State)

- Infants profoundly weak
- Show steady improvement, half will gain ambulation
- Early supportive care imperative to maximise their long-term potential
  - Respiratory care
  - Nutrition
  - Ancillary input
  - Caution with anaesthetics – risk malignant hyperthermia
Spinal muscular atrophy

- Programmed cell death of the AHC
- Types 1, 2 and 3
- Genetic diagnosis available and prenatal counselling
- NO cure
Classic phenotype

- many centres are reliant on clinical and basic investigations to confirm the “diagnosis”
  • Proximal weakness
  • Bell shaped chest (*classic X-ray*)
  • Tongue fibrillations (*fibs on ECG*)
  • Distal tremor
  • Normal facial expression / eye movements
  • Normal intelligence
Approach - depends on type

- Type 1 (non-sitters < 1 yr) - supportive, not for ventilation
- Type 2 (sitters – 1-3 yrs) - Lots of physio, monitor the back, appropriate schooling …. Clever children - plan for the future …. 
- Type 3 (walkers ± 2-5 yrs) - diagnosis helps a lot – counselling
- Offer salbutamol to type 2 and 3.

Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Finkel RS, et al
Lancet. 2016

• Nusinersen alters splicing of SMN2 pre-mRNA and increases functional survival motor neuron (SMN)
• Open-label, phase 2, multiple intrathecal doses of nusinersen in patients with infantile-onset SMA
  • 20 participants

• INTERPRETATION:
  • Acceptable safety and tolerability, pharmacology consistent with its intended mechanism of action, and encouraging clinical efficacy.

• ETHICS OF THE COST AND ACCESS IMPLICATIONS.................
SMARD - Spinal muscular atrophy with respiratory distress

- Cognitively intact infant
- Diaphragmatic paralysis (3-6 mths)
- Distal weakness
  - Foot and wrist drop
  - Areflexia

- Features typical of SMARD 1 mutation (Spinal muscular atrophy with respiratory distress) / (SIANR - severe infantile axonal neuropathy with respiratory failure)

- IGHMBP2 mutation

Grohmann et al. Nature Genetics 2001; 29: 75-77
Wilmhurst et al., Muscle Nerve 2001
Further complications

- Premature adrenarche / ?precious puberty
- Episodes of autonomic dysfunction (pallor / flushes, abdominal bloating / dumping syndrome)
- Complete oral aversion – fully PEG fed.
Messages / Clues

• SMARD1 - most likely under-recognised NMD

• May have a juvenile form – spectrum of disease
• Longitudinal data evident – some plateauing.
• More complex phenotype with additional systemic involvement.

• Ethics of intervention – considering Mx of SMA 1

Bush A 2006 Intens Care Med
Found rapid decline clinical score until 2 years of age
Plateau in residual capabilities / or even improvement
Markedly heterogeneous clinical outcome.
Scores 3 mths of age positive linear correlation with outcome at 1 year and 4 years of age.
Survivors – 2/3 in kindergarten or school.
Riboflavin transporter deficiency

Brown-Vialetto-van Laere syndrome

• Rare clinical condition
  • auditory neuropathy
  • bulbar palsy
  • stridor
  • muscle weakness – axonal neuropathy
  • respiratory compromise - diaphragmatic & vocal cord paralysis

• Autosomal recessive condition
  • causative mutations in the riboflavin transport genes (SLC52A2 and SLC52A3)

• Responds to high dose riboflavin (50-80mg/kg/day)
  Bosch et al. Orphanet J Rare Dis 7:1, 2012
Duchenne Muscular Dystrophy / BMD

- X-linked condition
- 1 in 3600-6000 live male births
- Presents between 2 - 4 years
- Language delay
- Calf hypertrophy
- Waddling gait
- CK >10 000u/l
- NO CURE ..... 
- Diagnosis in ~60% molecular genetics
- Treatment symptomatic - physiotherapy, back, T-As, cardiac
Figure 1: Interdisciplinary management of DMD

Coordination of clinical care is a crucial component of the management of DMD. This care is best provided in a multidisciplinary care setting in which the individual and family can access expertise for the required multisystem management of DMD in a collaborative effort. A coordinated clinical care role can be provided by a wide range of health-care professionals depending on local services, including (but not limited to) neurologists or paediatric neurologists, rehabilitation specialists, neuromuscularists, paediatricians, and primary-care physicians. It is crucial that the person responsible for the coordination of clinical care is aware of the available assessments, tools, and interventions to proactively manage all potential issues involving DMD. ABG—arterial blood gas. ACE—angiotensin-converting enzyme. DMD—Duchenne muscular dystrophy. Echo-echocardiogram. ECG—electrocardiogram. GC—glucocorticoids. GI—gastrointestinal. MEP—maximum expiratory pressure. MIP—maximum inspiratory pressure. PCF—peak cough flow. ROM—range of motion.
Role for corticosteroids

- Start: clinically affected (~4-5 yrs)
- Vaccinate: varicella, pneumovax and influenza
  - Prednisone 0.75mg/kg/day
  - Deflazacort 0.9mg/kg/day
- NOT a cure BUT gain 2-3 years of ambulation
- Reduces risk of scoliosis and stabilises pulmonary function
- Review pts every 3 months
- Time to stop, either
  - when loose ambulation
  - continue for “cardiac benefits”

Markham et al Neuromuscular Disord 2008;
Dubowitz Lancet Neurol 2010
Pharmacogenetics and DMD
Premature stop-codon. (~6%)  
Intervention to permit “read-through”
Exon-skipping (~6%)
The reality ....with

- Multidisciplinary centralised care
- Scoliosis avoidance
- Prolonged ambulation (steroids, vitamin D, intensive stretches)
- Cardiac review (prophylaxis – ACE inhibitors)
- Screening for nocturnal hypoventilation – nocturnal BIPAP
- Survival beyond 30 years
Aims of care for NMD pts in LMICs

Diagnosis
• NMD conditions which are important / relevant?
  • Genetic counseling e.g. SMA
  • Targeted therapies e.g. Duchenne MD

Overall management
• Optimal motor capacity
• Avoidance of complications e.g. scoliosis, respiratory track infections, oromotor, nutritional challenges
• Planning optimal educational placement, orthotic devices
• i.e. “standard” not “state of the art / experimental”
Challenges for Africa
### Diagnoses

- Lack of training / experience
  - Dedicated neuromuscular centres lacking in Africa
- Access to investigations
  - From CSF to histology / immunohistochemistry to genetics
- Interpretation of results
  - NCS
- Training
  - Need for focused and structured training to enable early recognition / intervention
  - Skills for optimal interventions – home / community care
Management

• Therapists
  • Lacking over all Africa
  • Burden of disease dominates and pulls them away from NMD

• Equipment
  • Lack of access to wheelchair, orthotics etc

• Tracheostomy support
  • Most interventions / home ventilation programs are only effective if the parent / caregiver is trained

• Drugs
  • Need for reliable access and monitoring e.g. DMD
Genetics

• Diagnostics
  • Limited to a few centres in Africa – expensive
  • DMD, SMA and CMT1A

• Unique African expression
  • RYR1 mutations
  • Debate around SMA
  • CMT

• Counseling
  • Need to sensitive and culturally insightful counselors

• Therapeutics – ethics.....
  • E.g. exon skipping, translarna, nusinerisen....
Summary

• Burden of NMD in Africa is skewed towards acquired and communicable causes
• Layering effect complicates issue of recognition further
• Genetic NMD disorders are likely to be as prevalent as in HICs
  • Maybe slight variation in expression for some ancestries
Challenges faced

- Prevention
- Recognition / diagnosis
- Early ancillary intervention
- Counseling
- Ethics of screening and role of pharmacogenetic interventions.